

should be sought if in doubt. Chamomile is a popular remedy used to treat teething pains in babies. However, chamomile is known to contain allergenic sesquiterpene lactones and should therefore be used with caution. The administration of herbal teas to children is generally unwise unless used according to professional advice.<sup>(97)</sup>

**Older patients** A review has considered the available evidence on the use of several herbal medicinal products (St. John's wort, valerian, ginkgo, horse-chestnut, saw palmetto and yohimbe) by older patients.<sup>(98)</sup> Whilst the treatments may offer considerable benefits for a range of conditions, the review raised the need for caution, particularly with regard to potential drug-herb interactions and possible adverse effects, when herbal medicinal products are used by older patients.

**Patients with cardiovascular disease** Concerns have been raised about the use of herbal medicinal products for cardiovascular disease, in particular, because of the lack of scientific assessment and the potential for toxic effects and major drug-herb interactions.<sup>(99)</sup>

**Peri-operative use** The need for patients to discontinue herbal medicinal products prior to surgery has been proposed.<sup>(100)</sup> From the available evidence, it has been suggested that the potential exists for direct pharmacological effects, pharmacodynamic interactions and pharmacokinetic interactions with eight commonly used herbal medicinal products (echinacea, ephedra, garlic, ginkgo, ginseng, kava, St. John's wort, valerian). The need for physicians to have a clear understanding of the herbal medicinal products being used by patients and to take a detailed history was highlighted.

The American Society of Anaesthesiologists (ASA) has reported that a number of anaesthesiologists have noted significant changes in heart rate or blood pressure in some patients who have been taking herbal medicinal products, including St. John's Wort, ginkgo and ginseng, and has advised patients to tell their doctor if they are taking herbal products before surgery.<sup>(101)</sup>

**Herb-drug interactions** Generally speaking, limited information is available regarding interactions between herbal products and conventional medicines. However, awareness of this issue is increasing, and the potential for drug-herb interactions has been discussed.<sup>(102-105)</sup> Concerns have been raised in the literature about herbal medicines interfering with breast cancer treatment,<sup>(106)</sup> and potential interactions between herbal products and cardiac drugs.<sup>(107)</sup>

Instances of drug interactions have been tentatively linked, retrospectively, to the concurrent use of herbal medicines. The rationale for such interactions is often difficult to explain if knowledge regarding the phytochemical constituents of the herbal product, their pharmacological activity and metabolism are poorly understood. The emergence of significant problems associated with the ingestion of grapefruit juice concurrently with certain medicines has emphasised the fact that clinically relevant interactions between drugs and natural products (both herbs and foods) may occur.<sup>(108)</sup>

As with conventional drug interactions, herb-drug interactions may be pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions could result when a herbal drug and a conventional drug have similar or antagonistic pharmacological effects or adverse effects. These interactions are usually predictable from a knowledge of the pharmacology of the interacting herb and drug. Pharmacokinetic interactions could occur when a herb alters the absorption, distribution, metabolism or excretion of a drug (and vice versa). These interactions are not easy to predict.

As with all potential drug interactions there are particular concerns when patients are stabilised on conventional medicines, such as warfarin, digoxin, anticonvulsants (e.g. phenytoin) and ciclosporin that are known to have a narrow therapeutic window.

**St. John's wort** Since 1998 evidence has emerged from spontaneous reports and published case reports of the interactions between St. John's wort and certain prescribed medicines leading to a loss of or reduction in therapeutic effect of these prescribed medicines (*see* St. John's Wort).<sup>(11)</sup> Drugs that may be affected include indinavir, warfarin, ciclosporin, digoxin, theophylline and oral contraceptives. There have also been reports of increased serotonergic effects in patients taking St. John's wort concurrently with selective serotonin reuptake inhibitors (e.g. sertraline, paroxetine). Results of drug interaction studies have provided some evidence that St. John's Wort may induce some cytochrome P450 (CYP) drug-metabolising enzymes in the liver as well as affecting P-glycoprotein (a transport protein). Regulatory Authorities throughout the EU and elsewhere have issued advice to patients and healthcare professionals.

The evidence for and understanding of most drug-herb interactions is limited. An attempt can be made, however, to identify herbal ingredients that have the potential to interfere with specific categories of conventional drugs, based on known phytochemical and pharmacological properties of the herb, and on any documented adverse effects.

For example, herbs containing substantial levels of coumarins may potentially increase blood coagulation time if taken in large doses. Prolonged or excessive use of a herbal diuretic may potentiate existing diuretic therapy, interfere with existing hypo/hypertensive therapy, or potentiate the effect of certain cardioactive drugs due to hypokalaemia. Herbs which have been documented to lower blood sugar concentrations may cause hypoglycaemia if taken in sufficient amounts and interfere with existing hypoglycaemic therapy. An individual receiving antihypertensive therapy may be more susceptible to the hypertensive adverse effects that have been documented with, for example, ginseng or which are associated with the excessive ingestion of plants such as liquorice.

This approach has been used in drawing up Appendices 1–13 (pp. 497–506), which provide information on potential drug–herb interactions. Appendix 1 groups together various therapeutic categories of medicines that may be affected by a particular herb or group of herbs. Appendices 2–13 list herbal ingredients that are claimed to have a specific activity alphabetically within each Appendix, including laxative, cardioactive, diuretic, hypo/hypertensive, anticoagulant/coagulant, hypo/hyperlipidaemic, sedative, hypo/hyperglycaemic, hormonal, immunostimulant, allergenic or irritant. Some commonly occurring groups of natural products found within these 148 herbal ingredients contribute towards their activities, toxicities or adverse effects. Appendices 14–22 list those herbal ingredients that contain amines, alkaloids or have sympathomimetic anti-inflammatory or antispasmodic activities, coumarins, flavonoids, iridoids, saponins, tannins or volatile oils.

*Interactions of herbal products in therapeutic drug monitoring* There are also examples of herbal medicinal products which appear to cross-react with diagnostic markers in therapeutic drug monitoring, e.g. where the constituents of a Chinese medicine and *Eleutherococcus* cross-reacted with digoxin assays.<sup>(104)</sup>

*Reporting of adverse reactions to herbal medicinal products* It is essential that information on the risks associated with the use of herbal products is systematically collected and analysed in order to protect public health. In 1996, the UK MCA extended its 'Yellow Card Scheme' for adverse drug reaction reporting to include reporting of suspected adverse reactions to unlicensed herbal products. This followed a report from a UK Medical Toxicology Unit on potentially serious adverse reactions associated with herbal remedies. Twenty-one cases of liver toxicity,

including two deaths, were associated with the use of TCM.<sup>(82)</sup>

The need to further improve pharmacovigilance on herbal products was highlighted in a study of patients' perceived behaviour towards reporting adverse reactions.<sup>(109)</sup> The study found that patients would be less likely to consult their doctor for suspected adverse drug reactions (minor or severe) to herbal remedies than for similar adverse reactions to a conventional over-the-counter medicine. This illustrates the need for greater public awareness that adverse reactions can occur and that such reactions should be reported. It also highlights the need for healthcare professionals to take a detailed medical history including use of herbal products and to be aware that patients may be reluctant to provide information.

The Uppsala Monitoring Centre of the World Health Organization plays an important role in the international monitoring of adverse health effects associated with herbal medicines.<sup>(110)</sup> The Centre has carried out an analysis of the suspected adverse reactions to herbal medicines reported over a period of 20 years. In 21 (0.8%) of the 2487 case reports reported to occur with single-ingredient herbal products, the suspected adverse reaction had a fatal outcome. Three of these reports concerned intestinal perforation after administration of a senna-containing laxative, presumed to be prior to X-ray examination because of intestinal pathology. Three reports concerned respiratory failure in association with the use of psyllium mucilloid-containing products and three other of respiratory failure in association with ispaghula husk. One patient had an anaphylactic shock after the injection of a horse-chestnut extract. In the remaining cases no pattern was recognizable. The Centre has highlighted the need for improved reporting in particular with regard to the precise identity and composition of the products.

### Efficacy

Despite the growing popularity of herbal medicines world-wide there is a dearth of scientific evidence of efficacy. Indeed, many of the herbs used medicinally in Europe have a traditional reputation for their uses, but there is little scientific documentation of their active constituents, pharmacological actions or clinical efficacy. Examples of this group include avens, boneset, burdock, clivers, damiana, Jamaica dogwood, parsley piert, pulsatilla and wild lettuce. For other herbs, documented phytochemical data or pharmacological data from animal studies may provide a plausible basis for their traditional uses, but evidence of efficacy from clinical studies is limited.

The current emphasis on evidence-based medicine requires evidence of efficacy from rigorous random-

ised controlled trials. Where possible, the evidence is best evaluated by systematic reviews and meta-analyses of available clinical trial data, as such approaches minimise both selection bias and random error.

Such approaches are now being applied to herbal medicines. Reports of systematic reviews undertaken for a number of herbal ingredients, e.g. aloe vera, artichoke, echinacea, evening primrose, feverfew, garlic, ginger, ginkgo, ginseng, hawthorn, horse-chestnut, mistletoe, peppermint, saw palmetto, St. John's wort and valerian have been published.<sup>(111-113)</sup> Several systematic reviews have been prepared by the Cochrane Collaboration (the international association dedicated to preparing and maintaining systematic reviews of the effects of healthcare interventions).<sup>(114)</sup> Several reviews highlight that, in some cases, the evidence base is weak and studies are often flawed. In other cases, studies have been methodologically sound and evidence of efficacy has been compelling.

St. John's wort, a widely used herbal product, has been investigated in many clinical studies. Evidence from randomised controlled trials has confirmed the efficacy of St. John's wort products over placebo in the treatment of mild-to-moderate depression (*see* St. John's Wort).<sup>(11)</sup> There is, however, a need for further studies to evaluate efficacy compared with that of standard treatments, particularly newer antidepressant agents, in well-defined patient groups and conducted over longer time periods.

One of the fundamental problems characteristic of herbal medicinal products is that the individual herbal ingredients contain a vast array of chemical constituents. Further, herbal medicines traditionally involve mixtures of different herbal ingredients, although in developed countries, recent trends indicate that single-ingredient herbal products are becoming increasingly popular. Herbalists would argue that combinations of ingredients are designed to provide the best therapeutic outcome while reducing adverse effects and toxicity. Evidence is emerging that different constituents within a herbal preparation may contribute to the overall therapeutic effect of the product and that in some cases synergistic and additive effects play an important role.<sup>(115)</sup>

In most cases there is a lack of knowledge of the phytochemical constituents responsible for the claimed therapeutic effects. To further complicate matters, it is well known that herbal products derived from the same herbal drug can vary considerably in terms of their phytochemical constituents depending on the source of plant material, the manufacture of the extracts and formulation of the dosage forms. As a result, efforts to establish clinical efficacy are hampered by how far results for a specific product can be

extrapolated to other products containing the same plant but different extracts. Where the active constituents of a herbal ingredient are known it is possible and, in most cases, desirable to standardise the extract/product. The aim of standardisation is to obtain an optimum and consistent quality of a herbal drug preparation by adjusting it to give a defined content of a constituent or a group of constituents with known therapeutic activity. Examples of herbal drugs with constituents with accepted, known therapeutic activity are few. Herbs with documented activities (and known active constituents) include: senna, frangula (hydroxyanthracenes); belladonna (alkaloids) and horse-chestnut (saponins).

In the case of St. John's wort, early studies concentrated on the hypericin constituents but more recent work suggests that hyperforin and possibly flavonoids also contribute to the antidepressant properties.<sup>(11)</sup> Studies analysing St. John's wort products have reported differing contents of hypericin and hyperforin.<sup>(116,117)</sup> Furthermore, some products showed consistent batch-to-batch concentrations of hypericin and hyperforin, whilst others exhibited significant interbatch variability.<sup>(116)</sup>

Despite the dearth of documented clinical evidence for the effects of the majority of herbal ingredients, there is no reason why herbal medicinal products should not be available for use in minor conditions, providing that these are consistent with traditional uses and that the herbal ingredients are of suitable quality and safety. It would seem to be more appropriate to use those herbal ingredients for which documented phytochemical and pharmacological data support the traditional use. Herbal medicines intended for use in more serious medical conditions require evidence of efficacy to support their use.

## Herbal Medicinal Products of Current Interest

**Echinacea** Echinacea is widely used throughout Europe for the prevention and treatment of colds and other upper respiratory tract infections. A recent Cochrane review of 16 clinical trials has reported that the overall results suggest that some products may have an effect greater than placebo, but that overall the results were inconclusive (*see* Echinacea).<sup>(118)</sup>

**Garlic** Numerous studies and systematic reviews have investigated the effects of garlic preparations in lowering raised serum cholesterol concentrations (*see* Garlic). Generally, the studies report beneficial results for garlic. However the evidence at present is insufficient to recommend garlic as routine treatment for hypercholesterolaemia. One of the major problems in

assessing the evidence available on garlic is the wide variation in the chemical composition of the products available, compared with fresh garlic. Further controlled studies are needed using standardised preparations to investigate efficacy in reducing serum lipids, blood pressure, platelet aggregation and antimicrobial activity (*see* Garlic).

**Ginger** Some clinical studies have reported ginger to be an effective prophylactic against motion sickness, although subsequent studies have found ginger to be ineffective (*see* Ginger).

**Ginkgo** Ginkgo is widely used in France and Germany in authorised herbal medicinal products for the treatment of circulatory insufficiencies (peripheral and cerebral). Currently, no licensed herbal medicinal products containing ginkgo are available in the UK.

Several systematic reviews have been carried out analysing the available evidence on the effects of ginkgo in cerebral insufficiency, dementia, tinnitus and intermittent claudication (*see* Ginkgo). Overall the results suggest some beneficial effects, but further studies are needed.

**Ginseng** Ginseng is widely renowned for its adaptogenic properties in Eastern countries, where it is used to help the body cope with stress and fatigue, and to promote recovery from illness or imbalance such as hypertension or hypoglycaemia. Generally, it is only recommended to be used for certain individuals with specific illnesses. By comparison, in the UK, ginseng is mainly self-administered and taken in the form of tablets or capsules containing dried extracts of the root. Ginseng products available in the UK are sold as food supplements, often in combination with vitamins and minerals. A wealth of research describing a wide range of pharmacological activities, particularly on the hypothalamic and pituitary regions of the brain, has been documented for ginseng (*see* Ginseng).

**Saw palmetto** Saw palmetto is widely used in Europe, particularly in Germany, for symptoms associated with benign prostatic hypertrophy (BPH). In the UK, saw palmetto is licensed in a number of products for the symptomatic relief of short-term, male urinary discomfort. Results of clinical trials indicate that saw palmetto is a potential agent for the symptomatic treatment of BPH (*see* Saw Palmetto).

**Valerian** Valerian is widely used in Europe for nervous tension and for promoting sleep. The therapeutic indications proposed by the EMEA HMPWP include relief of temporary, mild nervous tension and temporary difficulty in falling asleep.<sup>(19)</sup> A systematic review

of randomised, double-blind, placebo-controlled trials of valerian reported inconsistencies in methodology between studies, and that the evidence for efficacy was inconclusive (*see* Valerian). It is unclear whether the active principles in valerian are associated with the volatile oil, the iridoid components termed valepotriates or with some other, as yet unidentified, group of constituents.

## Conclusion

The use of herbal medicinal products, including use in addition to or instead of conventional medicines, is continuing to increase. Healthcare professionals need to be aware that patients may be taking herbal medicinal products, and need to understand their effects and be aware of the potential problems associated with their use. This handbook provides the reader with factual information on almost 150 herbal ingredients present in herbal medicinal products in European and other developed countries. Herbal medicinal products can offer an alternative to conventional medicines in non-life-threatening conditions, providing they are of adequate quality and safety, and are used in an appropriate manner by suitable individuals.

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